PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 3 :
A61K 9/22, 9/26, 9/52
A61K 31/78

A1

(11) International Publication Number: WO 85/ 04099

(43) International Publication Date:
26 September 1985 (26.09.85)

(21) International Application Number: PCT/US84/00431

(22) International Filing Date: 21 March 1984 (21.03.84)

(71) Applicant: KEY PHARMACEUTICALS, INC. [US/US]; 18425 N.W. 2nd Avenue, Miami, FL 33169 (US).

(72) Inventor: HSIAO, Charles, H. ; 4890 104th Avenue, Cooper City, FL 33328 (US).

(74) Agents: WEGNER, Harold, C. et al.; 2030 M Street, N.W., P.O. Box 19542, Washington, DC 20036-0542 (US).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: SUSTAINED RELEASE ORAL DOSAGE FORM FOR NAPROXYN

(57) Abstract

Sustained release tablet and method for administration of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid over a prolonged period, a single administration of the sustained release tablet of the present invention providing a 24 hour administration of the drug. This oral sustained release dosage form is a tablet containing sufficient (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid to provide a sustained release over a prolonged period contained in granules formed into said tablet, said tablet consisting essentially of a plurality of compressed granules consisting essentially of from about 1 to about 30 parts by weight hydroxypropyl methylcellulose and about 1 to about 30 parts by weight polyvinylpyrrolidone and a lubricant for the granules, such as magnesium stearate. The oral sustained release dosage unit form permits a sustained release of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid over a period of about 24 hours, eliminating the need for dosing at different periods of the day.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BG	Bulgaria
BR	Brazil
CF	Central African Republic
CG	Congo
CH	Switzerland
CM	Cameroon
DE	Germany, Federal Republic of
DK	Denmark
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
HU	Hungary
IT	Italy
JP	Japan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
MC	Monaco
MG	Madagascar
ML	Mali
MR	Mauritania
MW	Malawi
NL	Netherlands
NO	Norway
RO	Romania
SD	Sudan
SE	Sweden
SN	Senegal
SU	Soviet Union
TD	Chad
TG	Togo
US	United States of America

SUSTAINED RELEASE ORAL DOSAGE FORM FOR NAPROXYN

Background of the Invention

The present invention relates to a sustained release preparation of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid (naproxen). Specifically, it relates to an oral dosage form which provides a release period suitable for single daily dosing while exhibiting good bioavailability.

(+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid is a well known and widely used medication for pain relief, both generally and for specific maladies such as arthritis. (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid is also suitable as an agent to relieve the periodic pains of menstruation.

Summary of the Invention

In accordance with a first aspect of the present invention there is provided a sustained release oral medication in dosage unit form for the delivery of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid over a prolonged period of time which comprises a therapeutically effective amount of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid to provide a sustained release thereof over said a prolonged period of time which is contained in compressed granules having from about 1 to about 30 parts by weight hydroxypropyl methylcellulose having a molecular weight of from about 20,000 to about 140,000 and about one to 30 parts by weight polyvinylpyrrolidone (povidone) having a molecular weight of from about 8,000 to about 630,000, more preferably 20,000 to

216,000, and a lubricant for said compressed granules. In a preferred embodiment, the weight ratio of hydroxypropyl methylcellulose to polyvinylpyrrolidone is from about 3:1 to about 1:1, and more preferably is about 1:1.

In a second aspect of the invention there is provided a method of providing a sustained release of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid, contained in granules formed into said tablet, over a prolonged period, said tablet consisting essentially of a plurality of compressed granules consisting essentially of from about 1 to about 30 parts by weight hydroxypropyl methylcellulose and about 1 to 30 parts by weight polyvinylpyrrolidone and a lubricant for said granules, such as magnesium stearate.

The oral sustained release dosage unit form permits a sustained release of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid over a period of about 24 hours, eliminating the need for dosing at different periods of the day.

Detailed Description of the Invention

Included in the tablet is hydroxypropyl methylcellulose in an amount of about 20 to about 200 mg, with 50 mg being preferred. The hydroxypropyl methylcellulose has a molecular weight of about 20,000 to about 140,000, preferably between about 70,000 and about 110,000. As preferred embodiments may be mentioned molecular weights of about 86,000 (Methocel K4M, Dow Chemical) and about 120,000 (Methocel K15M, Dow Chemical). Also included is polyvinylpyrrolidone, present in an amount of about 20 to about 200 mg, preferably about 50 mg. The polyvinylpyrrolidone has a molecular weight in the range of from about 8,000 to about 630,000, and more preferably from about 20,000

to about 216,000, with 40,000 being a particularly preferred embodiment (povidone).

The tablet also includes a lubricant such as magnesium stearate to aid in the tableting process. The magnesium stearate may be replaced with other suitable tablet lubricants.

The tablet to the present invention may vary widely in the amount of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid that is included. The therapeutic range of 250 to 1,000 mg per tablet is indicated for the treatment of pain of arthritis, dysmenorrhea and other conditions, with 750 to 1,000 mg tablets being preferred. The oral dosage form herein described provides a release period suitable for once a day dosing.

The following non-limiting examples serve to further illustrate the invention:

EXAMPLE I

Blended together are 500 gm (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid; 48 gm hydroxypropyl methylcellulose (mw = 86,000 (Methocel K4M, Dow); and 26 gm povidone (mw = 60,000). The blend is granulated with about 160 ml deionized water, and the resulting granules are then dried at 50°C and ground through a 14 mesh screen. The granulated mixture is lubricated with 5 gm magnesium stearate. The resultant granules are then compressed into capsule-shaped tablets, each weighing 555 mg and containing 500 mg (+)-6-methoxy-alpha-methye-2-naphthaleneacetic acid.

According to U.S.P II dissolution test methods in simulated intestinal fluid, the following data were collected:

Time (in hours)	Percent Released
1	10
2	17
4	33
6	48
8	64
10	78
12	92

EXAMPLE II

Blended together are 500 gm (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid; 25 gm hydroxypropyl methylcellulose (mw = 86,000 (Methocel K-4-M, Dow); and 25 gm povidone (mw = 40,000). About 180 ml deionized water is added to the polymeric blend and after intimate mixing the resulting granules are then dried at 50°C and ground through a 14 mesh screen. The granulated mixture is lubricated with 5 gm magnesium stearate. The resultant granules are then compressed into capsule-shaped tablets, each weighing

1,110 mg and containing 1,000 mg (+)-6-methoxy-alpha-methyl-2-napthaleneacetic acid.

According to U.S.P II dissolution test methods in simulated intestinal fluid, the following data were collected:

Time (in hours)	Percent Released
1	9
2	18
4	35
6	49
8	61
10	72
12	80

The sustained release of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid coupled with the relatively long half life of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid in the blood plasma demonstrate a 24 hour sustained release capacity in the in vitro conditions used in this example.

WHAT IS CLAIMED IS:

1. A sustained release oral medication in dosage unit form for the delivery of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid over a prolonged period of time which comprises a therapeutically effective amount of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid to provide a sustained release thereof over said prolonged period of time which is contained in compressed granules having from about 1 to about 30 parts by weight hydroxypropyl methylcellulose having a molecular weight of from about 20,000 to about 140,000 and about 1 to about 30 parts by weight polyvinylpyrrolidone having a molecular weight of from about 8,000 to about 630,000, and a lubricant for said compressed granules.

2. A sustained release oral medication of claim 1, wherein the weight ratio of hydroxypropyl methylcellulose to polyvinylpyrrolidone is from about 3:1 to about 1:1.

3. A sustained release oral medication of claim 1, wherein the weight ratio of polyvinylpyrrolidone to hydroxypropyl methylcelluose is about 1:1.

4. A sustained release oral medication of claim 1, wherein said hydroxypropylmethyl cellulose has a molecular weight of from about 70,000 to about 110,000.

5. A sustained release oral medication of claim 1, wherein said polyvinylpyrrolidone has a molecular weight of from about 20,000 to about 216,000.

6. A sustained release oral medication of claim 1, wherein the polyvinylpyrrolidone has a molecular weight of about 40,000.

7. A method of providing a patient in pain with a sustained dosage of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid over a prolonged period of time which comprises orally administering to said patient a

tablet consisting essentially of a therapeutically effective amount of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid to provide a sustained release thereof over said a prolonged period of time which is contained in compressed granules having from about 1 to about 30 parts by weight hydroxypropyl methylcellulose and about 1 to about 30 parts by weight polyvinylpyrrolidone and a lubricant for said compressed granules.

8. A method of claim 7, wherein the weight ratio of hydroxypropyl methylcellulose to polyvinylpyrrolidone
is from about 3:1 to about 1:1.

9. A method of claim 7, wherein the weight ratio of polyvinylpyrrolidone to hydroxypropyl methylcellulose is about 1:1.

10. The method of claim 7, wherein a substantially constant plasma level of (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid is maintained over said prolonged period.

11. A method of claim 7, wherein said hydroxypropyl methylcellulose has a molecular weight of from about 20,000 to about 140,000.

12. A method of claim 7, wherein said polyvinylpyrrolidone has a molecular weight of from about 8,000 to about 630,000.

13. A method of claim 7, wherein said polyvinylpyrrolidone has a molecular weight of about 40,000.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US84/00431

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC [3]

A61K 9/22 A61K 9/26
A61K 9/52 A61K 31/78

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/19, 32, 81

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [5]

Computer Search : CAS Online 67-82 (hydroxypropyl methylcellulose or methocel) and polyvinylpyrrolidone

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X,Y	US, A, 4,308,251, published 29 December 1981 Dunn et al.	1-13
Y	US, A, 4,001,390, published 4 January 1977 Ohno et al.	1-13
Y	US, A, 4,389,393, published 21 June 1983 Schor et al.	1-13

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
31 May 1984	08 JUN 1984
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	

Form PCT/ISA/210 (second sheet) (October 1981)